# Treatment of Postherpetic Neuralgia

JMAJ 47(11): 529–536, 2004

Akira OZAWA

*Professor and Chairman, Dermatology, Course of Specialized Clinical Science, Tokai University School of Medicine*

**Abstract:** Herpes zoster, a commonly seen condition in daily medical practice, is reported to occur in 10–20% of the population at some time during the lifespan. Chronic, intractable postherpetic neuralgia, a sequela of herpes zoster, presents a clinical challenge. In recent years, effective antiviral agents that can be used in the outpatient setting have been developed for the treatment of herpes zoster and have achieved good clinical efficacy. However, in the absence of any clear, decisive treatment for postherpetic neuralgia, a variety of therapies have been elaborated for use in clinical practice. This paper outlines the treatment of postherpetic neuralgia and introduces therapeutic iontophoresis, which we have been using with success in the clinical setting. The prevention and prediction of postherpetic neuralgia is also discussed.

**Key words:** Herpes zoster; Postherpetic neuralgia (PHN); Antiviral agents; Iontophoresis therapy

## Introduction

Herpes zoster, a commonly occurring condition, is frequently encountered in the dermatology clinic and various other clinics. It is reported that the annual number of patients is 140–180 per 100,000 population and that 10–20% of the population suffers from this disease at some time during the lifespan. In Japan, approximately 500,000 people are affected by herpes zoster each year, and the total number of individuals affected is as high as 20 million.

Although herpes zoster is not life-threatening, it poses the clinical problems of severe neuralgia as a manifestation of the disease and chronic persistent postherpetic neuralgia (PHN), which follows the successful treatment of eruptions. PHN naturally does not occur in every patient with herpes zoster,[1)] although its incidence increases with age, particularly at about 60 years of age and above. The incidence of PHN is about 5% among patients with herpes zoster in their 60s, reaching about 10% among those in their 80s. In Japan, people aged 65 years or older already number 23 million, accounting for 18% of the total population.

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 129, No. 8, 2003, pages 1259–1264).
The Japanese text is a transcript of a lecture originally aired on December 2, 2002, by the Nihon Shortwave Broadcasting Co., Ltd., in its regular program "Special Course in Medicine".

Table 1 Treatments of Postherpetic Neuralgia in Japan

| Therapeutic modality | | Dosage | Efficacy, adverse effects, characteristics, and others |
|---|---|---|---|
| **Drug Therapy** | | | |
| ● Systemic therapy | | | |
| Nonsteroidal anti-inflammatory drugs | | Usual oral dose. The dose is increased or decreased depending on symptoms. Suppositories are widely used. | Because the effectiveness of prolonged treatment is poor, care must be taken so as not to continue oral treatment for too long. Care must also be taken because these drugs cause various side effects when doses orally. |
| Antidepressants | Tricyclic | Clomipramine (25～75 mg/day) | Effective in 10 out of 12 cases, with side effects in 4 |
| | | Others including amitriptyline (30～150 mg/day) imipramine, and nortriptyline (10～30 mg/day) | |
| | Others | Carbamazepine (an antiepileptic agent) | Little efficacy, with side effects that pose problems |
| Extract of inflammatory rabbit skin inoculated with vaccinia virus | | Neurotropin (__units/day divided into one morning and one evening dose) | Patients more than 6 months after onset of herpes zoster are amenable. Care must be taken not to continue therapy if there has been no response for 4 weeks. |
| Interferon | | $4～50\times10^4$ units/kg/day | The incidence of PHN and the duration of neuralgia were reduced. |
| Chinese medicines (combined with nerve blocks) | | Herbal extracts, Keisi-ka-zyutsubuto, 5 g, processed Japanese aconite daughter root powder, 1～5 g | 70～80% improvement (in 1 case) |
| | | Toki-sigyaku-ka-gosyuyu-shokyoto | Effective in 5 out of 12 cases |
| Antiarrhythmic drugs | | Mexiletine hydrochloride | Alleviation in 10 out of 11 cases |
| Others | | Antiviral agents (vidarabine, acyclovir, and others have been reported to be effective in preventing the development of PHN, but there is a tendency to rule out their efficacy for PHN itself), vitamin $B_{12}$, antiparkinson drugs (L-DOPA), immunoglobulin (intravenous infusion at high doses). | |
| ● Topical therapy | | | |
| Nonsteroidal anti-inflammatory drugs | Aspirin | 20 m*l* of a solution prepared by dissolving 50 g of aspirin in 1,000 m*l* of chloroform is applied topically 2～3 times weekly. | Alleviation in 5 out of 10 patients receiving 5～60 treatments |
| | | 2% aspirin ointment, ODT after application of 15 g | Alleviation in 5 cases. The effect lasted for 3～6 hours. |
| | Others | Indomethacin and others | Although this preparation is used widely because it is easy to apply, its efficacy is variable. |
| Capsaicin | | 0.025% capsaicin cream, 5 times daily | Effective in 12 out of 14 patients who had been treated for 4 weeks. Application causes a burning sensation. |
| | | Capsaicin cataplasms. It is applied twice a day. | Symptomatic improvement achieved in 8 out of 10 cases. Treatment caused a burning sensation. |
| Local anesthetics | | Xylocaine jelly | |
| | | 10% lidocaine cream (to be applied 3～5 times daily) | Alleviation in 5 of 10 patients receiving 5～60 treatments |
| | | Lidocaine tape (containing 60% lidocaine) | Effective for 12 hours |
| Others | | Nitrates (Isosorbide dinitrate is problematic because it causes headache.), topical anesthetics (Xylocaine jelly and others), and others | |

Table 1 Treatments of Postherpetic Neuralgia in Japan *(continued)*

| Therapeutic modality | | Dosage | Efficacy, adverse effects, characteristics, and others |
|---|---|---|---|
| **Physical Therapy** | | | |
| Nerve blocks | | The sympathetic, stellate, and somatic ganglions are blocked with local anesthetics 10～30 times, and if necessary, more than 100 times. As a rule, nerve blocks are administered at frequencies from daily to twice a week. In some cases, nerve blocks are administered by continuous infusion. Nerve blocks are administered in combination with other therapies such as epidural blocks and acupuncture in some cases. | Effective in 40～65% of PHN cases. With PHN lasting for more than 1 month, the efficacy decreases as the duration increases. In PHN lasting more than 1 year, it is almost ineffective. The younger the patient and the earlier the treatment, the more effective it is. It requires some skill. |
| Epidural blocks | | Local anesthetic agents are used alone or in combination with steroids. A course consists of 10 blocks given twice a week or it is administered by continuous infusion. | It showed little effect in some studies, but produced improvement in more than 80% of patients treated in other studies. The longer PHN has lasted, the less effective it is. |
| Subarachnoid blocks | | Injection of phenol or alcohol | Not adequately effective. The procedure is complicated. It may cause complications. |
| | | Injection of 0.1～0.2 m*l* of 10% tetracaine solution | Effective in 11 out of 14 cases. Blood pressure was decreased in 2. Respiratory depression |
| Intravenous infusion | | Infusion of 0.5% procaine | Effective, but not in all cases |
| Topical instillation | | Injection into the painful site. Dibucaine; dibucaine and benzocain; camphor and sodium salicylate; triamcinolone and procaine; and others | The effect is transient. |
| Acupuncture | | Anesthesia by acupuncture or with needles left inserted. Daily to once every three days for a total of about ten times | Anesthesia by acupuncture seems to be more effective. Efficacy rate: 36%. Effective in 96% if administered within 2 weeks after the onset. Skill is required. It is less painful for the patient. |
| Iontophoresis | | A pad soaked with a solution of lidocaine and methyl predni-solone is applied to the skin. A weak electric current is applied through the pad so that the drugs penetrate into the skin. The electric current is applied for about 30 minutes. The treatment is administered at intervals of 2～6 weeks for a total of up to 5 times. | Pain was alleviated by ≥40% in 2/3 of the patients who received it 3.8 times on average. The procedure is not painful. The efficacy is independent of the duration of PHN. It is effective even if other forms of therapy are ineffective and in patients having underlying diseases. The procedure is simple. |
| Cryotherapy | Dry ice | After local anesthesia, a piece of dry ice is pressed onto the site. | Effective in 77% of the patients who received it 1～14 times (mean: 5.7 times). It causes frost-bite which gives rise to vesicles and pain. |
| | Liquid nitrogen | Apply liquid nitrogen with a cotton ball once or twice a week or once a day for 2 weeks, and then once or twice a week | Effective in 70～80% of patients treated 4～20 times. |
| Transepidermal nerve stimulation (TENS) | | An active electrode attached directly to the skin is used to apply low frequency electric current (low frequency therapy). An implanted electrode is used to stimulate the spinal cord or the brain. | Effective in 78%. Transcutaneous nerve stimulation can be performed by the patients themselves and is useful as a home therapy for long-standing neuralgia. |
| Near infrared irradiation | | Infrared light at a wavelength of 700～1,700 nm (mainly 970 nm) is irradiated for 30 minutes (temperature at the surface of the skin: 39°C). | Effective immediately after irradiation in 39 out of 64 patients, and effective in 12, 24 hours later, without side effects |
| Laser therapy | | A GA-AI-As semiconductor laser is irradiated for about 10 minutes once a week for a total of 10～50 times. An Nd-YAG laser, a low reactive laser, and others are also used. | Effective in 50～90% |
| Others | | Moxibustion (pain disappeared when it was repeated 8 times), surgery (interruption of the posterior root or sympathetic trunk, and others), skin excision (effective in some studies, but seldom satisfactory), radiofrequency thermocoagulation (may be effective in patients not responsive to other therapies), electroconvulsive therapy (pain reduced by an electric current of 110～115 V, applied for 5 seconds to the anterior temporal area under general anesthesia, 1～2 times weekly to a total of 6-12 treatments), and others | |

(Source: Reference 5: *Dermatology Practice 10*, Bunkodo, 2000; pp. 110–114)

Thus, there is concern that the prevalence of herpes zoster and PHN will increase further.

In recent years, effective antiviral agents developed for the treatment of herpes zoster have been used in outpatient clinics with favorable clinical results.[2] However, no decisive treatment for PHN exists, necessitating various clinical elaborations for its treatment (Table 1). Various attempts to treat PHN are outlined below.

## What Is PHN?

Postherpetic neuralgia is defined by the International Association for the Study of Pain as chronic pain following resolution of acute herpes zoster that is accompanied with skin degeneration in the affected dermatome.

Another view advocates that neuralgia following herpes zoster should be collectively considered postherpetic pain (PHP), in which PHN is only one constituent. This view regards PHN as "deafferentation pain due to nerve degeneration."[3] According to this theory, transition to PHN is presumed to occur about one month after the onset of herpes zoster and to persist thereafter. However, in many cases of herpes zoster, neuralgia as a form of PHP may be present for 2–3 months after the successful treatment of eruptions, and therefore, it is difficult to form a clear distinction between PHP and PHN.

Under these circumstances, PHN cases present an issue in evaluating the clinical efficacy of a particular treatment. Consultation among anesthesiologists and dermatologists in Japan has resulted in the recommendation that, when examining the efficacy of treatment for PHN, patients be examined at least 3 months after the onset of herpes zoster.[4]

## Treatment of PHN

### 1. Current status and expected efficacy of anti-pain procedures

Surveys of anti-pain procedures used for PHN were carried out in Japan in 129 accredited facilities of anesthesiology and 259 accredited facilities of dermatology by the respective academic societies.[4] On the basis of these surveys, the current status and expected therapeutic efficacy of various anti-pain procedures for PHN were investigated and a report issued.

According to the report, therapies noted for their therapeutic efficacy and frequent clinical use include NSAIDs, psychotropics, and nerve block therapy. Therapies from which high efficacy was expected despite limited actual use included narcotic analgesics, steroids, laser therapy, iontophoresis, psychotherapy, and rehabilitation training.

However, no clear treatment has been established for PHN, although various procedures have been elaborated and employed.

### 2. Treatment policies for PHN

The basis of treatment for PHN consists of medical intervention and detailed instructions given to individual patients and their families.[5] Medical treatment alone often may be insufficient.

**(1) Instructions for daily life**

i) Patients should not be made anxious or given preconceived ideas about pain and PHN at the onset of herpes zoster.

ii) Patients should be instructed to return to normal daily activities after eruptions have been cured. In principle, there are no restrictions on daily life activities.

iii) Instructions in the creation of a pain-free environment should be given to patients and their families. Suggestions should be based on the patient's lifestyle, circumstances, personality, and relationships with family members.

**(2) Medical treatment**

i) Since no decisive treatment currently exists, the status of pain should be assessed objectively and treatment chosen according to the individual patient.

ii) A combination of several treatments may be necessary in some cases depending on

symptoms.

iii) The treatment chosen should be evaluated frequently to avoid its continued use merely because the patient complains of pain.

**(3) Choice of medical treatment**

Treatment should be chosen for each patient according to his or her symptoms and phase of illness. The goal of treatment should be to restore the patient's ability to carry out daily activities such as eating, sleeping, and so on. Antiviral agents are unlikely to have therapeutic efficacy for PHN.

i) Up to 3 months after the cure of eruptions

Although neuralgia as a form of PHP remains in many patients, the degree of its severity gradually decreases. Therefore, if there is no serious impediment to daily living, symptomatic treatment with NSAIDs and vitamin B preparations should constitute the core treatment. When there is severe pain, aggressive anti-pain procedures including physical therapies such as nerve block should be employed.

ii) Up to 6 months after the cure of eruptions

Drug treatment using NSAIDs, vitamin B preparations, or antidepressant drugs, and physical therapy including nerve block therapy, laser therapy, acupuncture, and iontophoresis therapy should be tried as monotherapy or combined therapy.

iii) More than 6 months after the cure of eruptions

Combined therapy including drug treatment and physical therapy should be employed, while exercising caution with regard to the possible adverse effects of prolonged use.

**(4) Treatment of elderly patients**

Elderly patients account for a considerable proportion of all patients with PHN. Particular attention to the following points is important in the treatment of this population.

i) Is it truly PHN?

It is possible that any pain in patients who have had herpes zoster may be wrongly attributed to PHN. Fracture pain, osteoarthritis, secondary muscle ache derived from pain-limited motion, and pain from other diseases such as cardiac disease may be reported as PHN by the patient.

ii) Psychological dependence

Patients with PHN tend to be isolated from social life, preoccupied with pain and the fear of pain, and psychologically dependent on others. It therefore is necessary for patients and their families to better understand the patient's response to pain and to reconsider the living environment.

iii) Assessment of pain

The assessment of pain in elderly patients can be difficult, often leading to difficulties in understanding symptoms. The physician should strive for objective assessment of the patient's pain, taking into account his/her speech and actions in the consultation room or reports from family members regarding the patient's daily life.

iv) Dependence on treatment

Elderly patients characteristically exhibit intense anxiety in regard to the cessation or alteration of treatment. The physician in charge should always try to assess the patient's pain objectively and make certain that the patient understands the need to continue, change, or terminate treatment.

**(5) Iontophoresis therapy for PHN**

Iontophoresis therapy is a method of topical drug delivery by which ionized drug in a solution is introduced into the body painlessly via the skin.

We have carried out iontophoresis therapy using lidocaine and methylprednisolone in the Department of Dermatology, Tokai University School of Medicine (Fig. 1), with favorable clinical results. Over two-thirds of more than 1,000 patients with PHN (mean duration of PHN, 30.6 months) showed 40–100% improvement in neuralgia after an average of 3.8 sessions of therapy.[5)]

This form of therapy is painless, and its efficacy is not affected by the duration of PHN. The treatment was effective in patients with

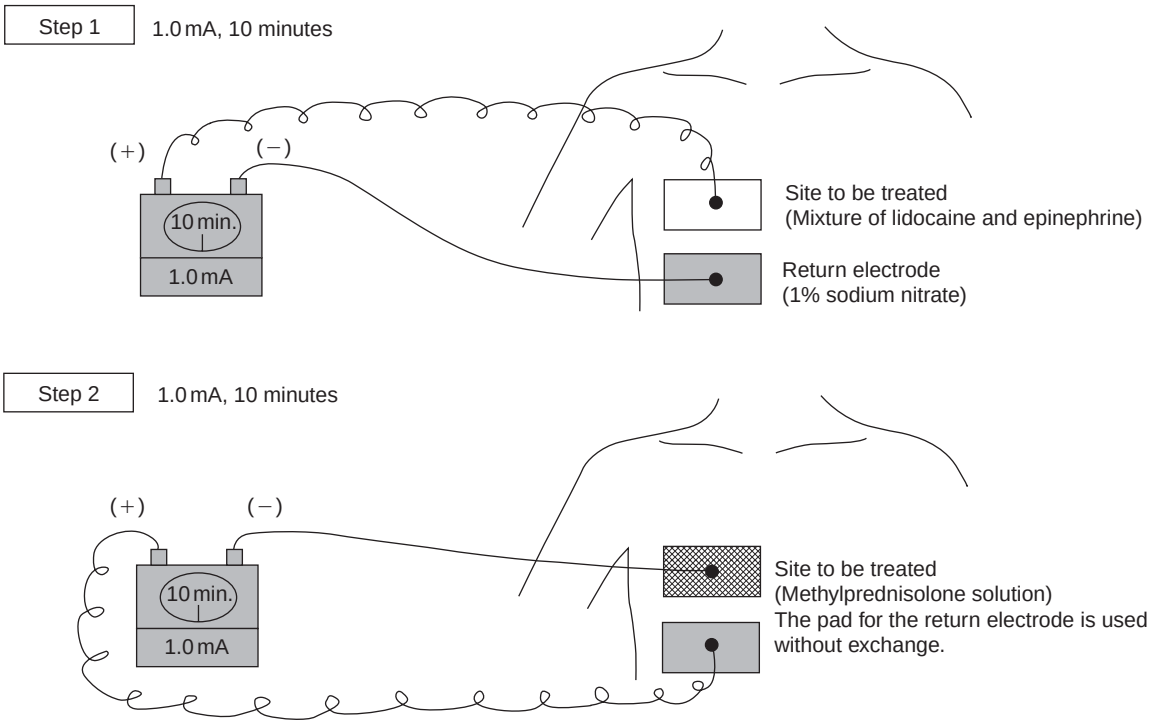


Fig. 1 Iontophoresis for postherpetic neuralgia
(Source: Reference 5: *Dermatology Practice 10*, Bunkodo, 2000; pp. 110–114.
For Information about the instrument, refer to BS Medical, Tel. +81-3-3299-6425.)

pain persisting for more than one year, those who did not respond to other treatments, and those who had underlying diseases such as malignant tumor, hypertension, or diabetes mellitus. Follow-up of patients for 1–5 years after the end of therapy confirmed a continuing therapeutic effect.[6)]

Therefore, iontophoresis therapy for PHN is a clinically useful therapeutic option. Many other therapies have been reported to be less effective in patients with neuralgia persisting for at least one year, indicating the usefulness of iontophoresis therapy for the treatment of PHN.

## Is Prevention of PHN Possible?

Unfortunately, there is currently no absolute prophylaxis for PHN. However, since PHN occurs as a sequela to herpes zoster, the prevention of herpes zoster is useful.

### 1. Prevention of herpes zoster

Varicella vaccine is promising, and those who are of an age susceptible to herpes zoster, i.e., 50–55 years of age, should be inoculated with varicella vaccine to obtain booster immunity.[7)] Clinical trials of this procedure have been carried out in the US as well as Japan, with benefits reported.

### 2. Prevention of PHN in herpes zoster

Prevention of the occurrence of PHN is an important issue to be considered when a patient has already contracted herpes zoster.

#### (1) Antiviral drug therapy in the early phase of herpes zoster

Herpes zoster should be mitigated through early-phase antiviral drug therapy.[8)] Antiviral agents with excellent clinical efficacy have been developed, including Arasena A® ointment as topical therapy, Zovirax® and Barutorex® as oral preparations, and Arasena A® and

Table 2 Immunogenetic Analysis of VZV

| | |
|---|---|
| Herpes zoster | Disease resistance: HLA-B*5101 |
| PHN | Disease resistance: HLA-B*4001<br>Disease resistance: HLA haplotype (A*3303-B*4403-DRB1*1302) |

Zovirax® as intravenous preparations. The main point of treatment is to use these antiviral agents in the early stage after onset. One report has documented a 50% decrease in the incidence of PHN after antiviral drug treatment for herpes zoster.

In dosage regimens of antiviral drug therapy, renal function is an important issue. Dose adjustment is necessary for elderly patients or those who have renal disease. Dosage regimens of intravenous formulations are described in detail in the manufacturer's instructions for use of the drug, and the treatment of patients should follow these instructions. When impaired renal function is present, the dose is determined according to serum creatinine clearance. In actual practice, serum creatinine clearance can be estimated from the serum creatinine level and the patient's body weight and age according to a simple formula.[2)]

It should be noted that the combined use of topical and oral antiviral drugs or topical and intravenous drip administration generally is not covered by health insurance in some areas of Japan (e.g., Kanagawa Prefecture).

**(2) Proper topical therapy for skin lesions**

Dermatologists should select an appropriate topical preparation for eruptions, with reference to the particular disease stage, and provide instructions as to its use.[2)]

**(3) Aggressive treatment of neuralgia**

Neuralgia should be treated as needed, in cooperation with an anesthesiologist.

**(4) Instructions for daily life**

For patients with herpes zoster, instructions for daily life that emphasize the importance of rest, recreation, and nutrition are necessary. In addition, patients should be instructed to return to their usual everyday life after eruptions have subsided. Rehabilitation training should also be considered in some cases, particularly those with limb lesions.

## Prediction of Onset of Herpes Zoster and PHN

If PHN derives from nerve degeneration resulting from invasion of varicella-zoster virus (VZV), the body's immune response (sensitivity) to VZV may be involved in disease onset. If there were immunogenetic differences in patients affected by varicella, zoster, and PHN, and if such differences were clarified, the onset of disease might be predicted.

In this regard, we examined the HLA antigen gene region on the short arm of chromosome 6 for genetic control of the immune response to VZV.[9)] Results confirmed the involvement of HLA antigens in disease susceptibility and genes controlling resistance (Table 2). Therefore, if these diseases can be predicted, prevention of their onset may become possible by various means, including vaccination.

## Conclusion

Antiviral agents for herpes zoster have been developed and are in widespread use in clinical practice, although the efficacy of these antiviral agents for PHN has been denied. However, methods of dealing with patients and the usage and place of antiviral agents in the actual clinical setting should be considered further, taking into account both the prediction and prevention of the onset of herpes zoster and PHN.

## REFERENCES


1) Iizuka, M. and Ozawa, A.: Diagnosis and treatment of postherpetic neuralgia. *Monthly Book Derma* 1999; 28: 38–40. (in Japanese)
2) Mabuchi, T. and Ozawa, A.: Appropriate dosage regimen of antiviral drug therapy and instructions for active daily living after cure of eruptions. *Rinsho To Yakubutsu Chiryo* 2001; 20: 1046–1050. (in Japanese)
3) Miyazaki, T.: What is postherpetic neuralgia? *Q & A in Diagnosis and Treatment of Herpes* (ed. Niimura, M.) Research Institute of Clinical Therapeutics and Medicine, Tokyo, 1993; pp. 196–197. (in Japanese)
4) Miyazaki, T.: Report of a questionnaire survey on the concept of herpes zoster-related pain. *Pain Control of Herpes Zoster* (ed. Miyazaki, T. *et al.*) Torre Lazur McCann, Tokyo, 1999; pp. 5–10. (in Japanese)
5) Sasao, Y. and Ozawa, A.: Postherpetic neuralgia. *Dermatology Practice 10: Difficult-to-Treat Skin Diseases* (ed. Hashimoto, K. *et al.*) Bunkodo, Tokyo, 2000; pp. 110–114. (in Japanese)
6) Ozawa, A. *et al.*: Follow-up of clinical efficacy of iontophoresis therapy for postherpetic neuralgia (PHN). *J Dermatol* 1999; 26: 1–10.
7) Levin, M.J. *et al.*: Use of a live attenuated varicella vaccine to boost varicella-specific immune responses in seropositive people 55 years of age and older: duration of booster effect. *J Infect Dis* 1998; 178, Suppl 1: S109–S112.
8) Ozawa, A.: Treatment of herpes zoster. *Nippon Ishikai Zasshi* 1997; 117: 1749–1753. (in Japanese)
9) Ozawa, A. *et al.*: HLA A 33 and B 44 and susceptibility to postherpetic neuralgia (PHN). *Tissue Antigens* 1999; 53: 263–268.